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(56) Documents Cited
WO 97/26895 A WO 94/27611 A WO 94/14423 A
WO 93/11753 A

(58) Field of Search
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(54) Abstract Title
Solvent compositions for gelatin capsules

(57) The invention relates to the preparation of stable concentrated solutions of poorly soluble drug substances (including peptides and proteins) for encapsulation into soft gelatine and two piece hard gelatine capsules.

The solvent compositions comprise

(a) diethylene glycol mono-ethyl ether, soya lecithin water, soya bean oil, polyethylene glycol-glycerol linoleate and polyethylene-glyceryl caprylate/caprate;

(b) diethylene glycol mono-ethyl ether, PEG 400, Tween 40, Labrafil and ammonium acetate in water, (TWEEN and LABRAFIL are Registered Trade Marks);

(c) N-methyl pyrrolidone, povidone C15 and water.

The preferred drug is ibuprofen.

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Solubilising systems for difficult pharmaceutical actives for preparing concentrated stable solutions for encapsulation into soft gelatine and two-piece hard gelatine capsules

Background to Invention

Generally it is difficult to prepare concentrated solutions of poorly soluble drugs which are stable for manufacture of small size capsules. Most liquids can not be filled in gelatine capsules. In particular water greater than 20% dissolves the capsule shell. Many liquids like Propylen glycol, glycerin, low molecular weight alcohols, acids, ketones and esters can not be filled in gelatine capsules and therefore can only be added in small amounts due to the pH parameters of the fill materials. The pH below 2.5 hydrolyse the capsule shell and pH above 7.5 tannes the shell resulting in leakage or decreased solubility of the system. The oil/water or water/oil emulsions also dissolve capsule shell.

The problems are also encountered with suspensions which must be of particular size (no more than 80 mesh) as coarser suspensions cause improper functioning of the equipment and good contents uniformity throughout the batch.

The drugs in solution give good contents uniformity and faster dissolution when injested. However, formulators had faced problems of dissolving the drug in small amount of the solvent or oil to produce a capsule small enough for patient's aceptance and feasible for manufacturing on economics basis.

Weber & Molenaur US Patent Number 3,557,280 describes the preparation of aq. solution of oxytetracycline in water containing small amounts polyvinylpyrrolidone/ and magnesium sulphate and pH adjusted to 8-9.5 by addition of sodium hydroxide or ammonia. The solutions were prepared for intravenous injections and syrups for pediatric formulations. Gardella et al US Patent Number 4,002,718 used polyvinylpyrrolidone/ or glycerin to increase dissolution of digoxin polyethylene glycol.

Yu et al US Patent Number 5,360615 (1994) use NaOH and KOH to dissolve acidic drugs eg Ibuprofen, Naproxen and Indomethacin and use HC1 to dissolve basic drugs eg Cimetidine.

CLAIMS:

1. The inventor claims new methods of preparation of concentrated solutions of drug substances which are difficult to dissolve.

2. The inventor claims that concentrated solutions of drug substances prepared by new methods are stable and suitable for encapsulation into softgel capsules and two piece hard gelatine capsules.
The concentrated solutions can be used to manufacture small size capsules.

3. The inventor claims solvent system containing Diethylene Glycol Monoethyl Ether(18-39%), Soya Lecithin (1-8%), Water DM(1-12%), Soya Bean oil(10-20%), Polyethylene Glycol-Glycerol linoleate and Polyethylene-Glyceryl caprylate/Caprate(1-2%) of the fill weight to dissolve the drug to give concentrated and stable solutions.

4. The inventor claims solvent system containing Diethylene Glycol Monoethyl Ether, Polyethylene Glycol 400, Tween 40, Labrafil and Ammonium acetate in water to give concentrated and stable solutions of drug substances.

5. The inventor claims solvent system containing N-Methyl-Pyrrolidone(10-60%), Povidone C15(5-20%) in Water DM(4-8%) using pharmaceutical active(1-40%) to concentrated and stable solutions.

6. The inventor claims pharmaceutical actives examined and included Ibuprofen, Ketoprofen, Naproxen, Fenbuprofen, Fenoprofen, Flurbiprofen, Cyclosporin, Calcitonin, Cimetidine, Indomethacin, Paracetamol and Insulin.
The highly concentrated solutions were prepared using art and methodology in mixing the ingredients.

7. The inventor claims additional pharmaceutical actives for use in solvent systems to include: analgesics, anti-inflammatory agents, antipyretics, beta-blockers, anti-diabetics, anti-bacterials, antibiotics, anti-virals, and nutritional supplements(including vitamins, minerals, fatty acids and amino acids etc.).

8. The inventor claims formulations of Ibuprofen concentrated solution encapsulated in soft gelatine and two-piece hard gelatine capsules.

INGREDIENTS	WEIGHT %
Ibuprofen	38.00
N-Methyl-Pyrrolidone	45.00
Povidone C15	8.00
Water DM	5.00

9. The inventor also claims formulation of Ibuprofen concentrated solution encapsulated in soft gelatine and two-piece hard gelatine capsules

INGREDIENTS	WEIGHT %
Ibuprofen	38.60
Diethylene Glycol Monoethyl Ether	38.00
Tween	13.50
PEG400	3.86
Labrafil	2.89
Ammonium acetate	1.54
Water DM	0.96

Average capsule fill weight per capsule 518mg as clear solution and coloured solutions.

The N-Methyl-Pyrrolidone(10-60%) containing Povidone C15 in DM Water(4-8%) increased the solubility of difficult solubilising pharmaceutical actives thereby enhancing their physico-chemical stability.

The enhanced solubility can be attributed to a complexing action with Nitrogen and carbonyl reactive centres of the molecule. This can be attributed to three parameters;

a) Non-polar molecular dimension
b) Polar type chemical bonding
c) Hydrogen bonding

This system also overcomes the heating methods to dissolve pharmaceutical actives. This method also overcomes the use of other co-solvents or surfactants and therefore is suitable for manufacturing smaller capsules for ease of swallowing.

TWEEN and LABRAFIL are Registered Trade Marks

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Claims searched: 3-5, 8 & 9

Examiner: Diane Davies
Date of search: 1 February 1999

Category	Identity of document and relevant passage		Relevant to claims
A	WO 9311753 A	(R.P. Scherer Corp.) Whole document: use of polethylene glycol and polyoxyethylen sorbitan esters as co-solvents for ibuprofen in capsules.	3,4,9

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.